to Gly119 of bovine growth hormone, wherein said variant has growth hormone inhibitory activity, with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

115 (new). The DNA molecule of claim 114 where said variant is a single substitution variant of a vertebrate growth hormone.

116 (new). The DNA molecule of claim 114 where the vertebrate growth hormone variant is a variant of a mammalian growth hormone.

117 (new). The DNA molecule of claim 114 where the vertebrate growth hormone variant is a variant of a human growth hormone.--

REMARKS

1. Description (OA §§6, 7)

1.1. We have deleted "purified or", from claims 10, 29, 66, 81, 107 and 109-112, so these claims no longer read on purified, naturally occurring molecules.

1.2. There is a suggestion at page 6, lines 3-5 that claim 81 would be allowable if "purified or" is excised. This amendment has been made. We would be willing to consider agreeing to an Examiner's amendment cancelling claims 10-45, 63, 65-80, and 99.

Since claim 81 is allowable, withdrawn species claims (e.g., 86 and 87) should be rejoined. Also, we have made method claim 88 dependent on 81. Hence, the method claims should be rejoined pursuant to MPEP §821.04.

1.3. The Examiner, on page 6, lines 7-11 proposes alternative claim language.

This language (including the allowed proviso) has been presented in new claim 114. Claims 115-117 further limit 114.

1.4. With regard to claims 82-85, we do not understand how they can be considered limitations "collected piecemeal from the

specification" and presented as a "single concept". Claims 82-85 couple a percentage identity limitation, applied either to helix 3 or to the whole GH sequence, with the base claim limitation of the position corresponding to Gly119 in bGH. Claim 82, for example, contemplates a helix 3 at least 50% identical to that of bGH or HGH. The percentage identity limitations of claims 82-85 are expressly taught at P14, L10-13 and P18, L6-12.

The specification plainly teaches that the critical step for making a GH mutant which is a GH antagonist is to replace the Gly corresponding to bGH G119 (or hGH G120) with an amino acid other than glycine or alanine. See P6, L36-P7, L4; P21, 19-24. It also plainly teaches that additional mutations are permissible, see P23, L5-9. These mutations may be, like bGH G119, within helix 3, see P14, L10-13; P22, L6-8 and 23-33, or outside it, see P18, L6-12; P17, L16-30.

The 50% helix 3 mutant contemplated by P14, L10-13 is a "GH antagonist", and hence must include the 119/120 mutation. The percentage identity mutants contemplated by P18, L6-12 are a preferred embodiment of the "substantially homologous" polypeptide defined by P17, L31-P18, L4, which is preferably a polypeptide defined by limitations (a), (b) "and/or" (c). Limitation (a) embraces the mutation at bGH 119, and (b) and (c) refer to (b) the substitution or deletion of nonconserved AAs, and (c) the truncation of 1-95 and/or 134-191. It should be noted that still other modifications are contemplated, see "but is not limited to" language at P17, L32-33, and the discussion of conservative substitution of conserved positions at P23, L14-15, P24, L20-22 and P26, L1-20.

1.5. At page 7, lines 3-11 of the office action, the Examiner maintains her criticism of "reference vertebrate growth hormone", and likewise criticizes "first vertebrate growth hormone".

Page 1, lines 16-21 of the specification states:

> This invention relates to novel muteins of growth hormone ("GH"), especially human growth hormone ("hGH"), which diminish,

> decrease or inhibit the growth of animals or otherwise diminish, decrease or inhibit the effects of endogenous GH by acting as an antagonist to growth hormone receptors ("GHRs").

The concept of a "mutein" requires that there be a reference protein and an allowed range of mutation therefrom. In the quoted passage, human GH is cited as a reference. Elsewhere, there are references to bovine GH (P6 L36, P13 L33, P17 L33, P22 L14), human GH (P13 L33, P17 L19, 33), and mammalian (P17 L19, 26) or vertebrate GHs generally (P13 L33, P17 L19, 26, P18, L5, P24 L10, 20, 25, P26 L23, P30 L4, P34 L27).

The term "first" GH or "reference" GH is introduced simply to make it clear that one is referring to the reference protein and not to the mutein. This is especially useful in situations where there is more than one reference protein, as in the case of a hybrid. Cp. P16, L29-P17, L15. Giving the reference protein an identifier like "first" or "second" does not add "new matter" or render the claims indefinite.

1.6. At page 7, lines 12-15, the Examiner states:

> Applicant's arguments in paper #24, page 14, are confusing, at best. It would appear that Applicant is arguing that because the various growth hormone molecules have a degree of amino acid identity, that claims to molecules having a particular degree of amino acid identity are described.

Actually, the preferred percentage identities of 50% and 80% are explicitly set forth in the specification, notably at page 18, lines 6-12:

> Preferably, the polypeptide is a least about 50% homologous, more preferably at least 80% homologous, with bGH or hGH in the subsequence substantially corresponding to the third alpha helix (approximately, residues 106-129) of bGH, and more preferably over the entire length of the polypeptide (ignoring extraneous non-bGH-related fusions to the amino-terminus or carboxy-terminus).

One percentage identity which is inferred is the 66% identity. This falls between the 50% and 80% disclosed above, and is the disclosed identity of bovine GH with human GH, see P14, L19-24. In view of the fact that bGH and hGH are the most preferred reference proteins (P13, L33; 14, L13; P17, L33; P18, L5-8) and specific mutants of both are taught, the recitation of an intermediate "at least 66%" claim appears justifiable.

The description requirement does not require that every claim limitation exactly echo the specification. Ralston Purina Co. v. Far-Mar Co., Inc., 222 USPQ 863, (D.Kan. 1984), aff'd in part and rev'd in part, 227 USPQ 177 (Fed. Cir. 1985). The Federal Circuit held that a total moisture content limitation of "at least about 25%" was supported by the express disclosure of soybean meal with 10-12% water and addition of 25% or 27% water, for total content of 35-39%. The limitation of "protein content of at least about that of solvent extracted soybean meal" (which was 50%) was supported by the disclosure that meals of 44%, 50%, 70% and 90% protein were standard. The limitations of temperature of "in excess of 212°F" and "into the range of 212-310°F" were supported by the disclosure of 212-380 in Example 1. In Kolmes v. World Fiber Corp., 41 USPQ2d 1829 (Fed. Cir. 1997), the claim to a rate of 8-12 turns per inch was supported by the disclosure of 4-12, with 8 being preferred.

The other inferred percentage identity is "90%", which was a compromise value based on rat (87%) and porcine (92%) GHs, see P14, L19-21. See new claims 116 and 117. It should be noted that 90% identity, in a protein of less than 200 a.a., implies a deviation of fewer than 20 a.a. Yet there are naturally occurring GHs which differ from bGH and hGH by more than 100 a.a.'s.

To the extent that the examiner is concerned by the failure to specify which AAs can be varied, it is noted that this is addressed in, e.g., claims 10 and 63.

1.7. With regard to 10% binding affinity (OA p. 8, 18-12), the specification plainly contemplates that a mutation could

reduce GH receptor affinity. P19, L30 to P20, L1 states:

> Preferably, the compounds of the present invention have an ED50 which is less than about 10 times the ED50 of wild-type bGH in an assay of the ability of the compound to displace radiolabeled wild-type bGH from a liver membrane preparation made as described below. More preferably, the compounds have an ED50 at least comparable to that of wild-type bGH. Most preferably, the compounds have a higher affinity for GHRs than does the GH native to the animal receiving the compound.

If the ED50 of the mutein is ten times that of wild-type bGH, then its affinity for the receptor is 10% that of wild-type bGH.

1.8. With regard to claim 19, we respectfully disagree with the examiner's interpretation of claim 19 as allowing non-conservative substitutions anywhere. It allows nonconservative substitutions only at residues corresponding to hGH 1-8, hGH 32-52, hGH 64-72, hGH 94-113, hGH 131-161 and hGH 190-191. That is 76/191 positions. The allowed nonconservative substitutions are further constrained by base claim 10(B)(II)(b).

To the extent that the Examiner urges that we should not enjoy coverage of <u>any</u> nonconservative substitution, we point out that it is plain from purview of the sequences of the GH family that numerous nonconservative substitutions are tolerated, see P26, L21-P28, L10. Thus, Lys is replaced in aligned sequences of the GH family by Ser, Thr, Ile, Glu, Gly, Asn, His, Val, Gln, Asp and Ala; only the His replacement is a conservative substitution. Cp. P27, L35-37 with P26, L1-10.

1.9. With regard to claim 29, the Examiner says that the specification "never pairs the 96-133 fragment with 50% identical".

At page 18, lines 2-3, the specification teaches "truncation of amino acids 1-95 and/or 134-191", which would leave a 96-133 fragment. P17, L35-37 contemplates coupling this truncation with substitution at an amino acid "not conserved among the vertebrate

GHs" (and note from P17, L32-33 that this is not limiting language, but language of preference). The 50% preference is set forth in the same paragraph, and can apply to the "entire length of the polypeptide" (which, if the polypeptide were obtained by truncating the wild-type GH, would be the 96-133 region). Plainly, the two limitations are paired in a disclosed embodiment.

1.10. With regard to claim 34, the specification is not directed merely to close mutants of bovine GH. Mutants of human GH appear in the examples, and they are only 66% identical to bGH.

The invention is broadly defined in terms of muteins of "growth hormone", not just bGH or hGH. See P1, L16-17. Specific references to mutants of "vertebrate GH" appear at P6, L33-35, P13, L30-33, P14, L10-13; P17, L16-19.

1.11. With regard to the exclusion of proline, Applicants specifically discloses a proline mutant, and hence may as easily excise it as include it. See In re Johnson, 194 USPQ 187 (CCPA 1977).

1.12. With regard to claim 38, the Examiner appears to be thinking of the language at P22, L11 ("acceptable alpha-helical propensities"). However P23, L15-19 speaks of increasing the alpha-helical propensities.

1.13. In OA §7, the Examiner explores the description issue of whether the 8 specifically disclosed sequences are representative of the claimed genus. The Examiner argues (1) the polypeptides can be as short as 50 amino acids, (2) conservation of AAs does not provide for predictability, and (3) alanine scanning mutagenesis shows that conservative substitutions can have drastic effect on activity. She says there is no known or disclosed correlation between structure and activity.

But the required correlation need not be perfect. The relevant question is not whether a mutant meeting the structural limitations could be inoperative, but rather whether the odds are good that it would be operative, as compared to those for a

random polypeptide. We disagree that the disclosed species are unrepresentative of the genus; the bGH and hGH ones are only 66% identical to each other.

2. Enablement

The reasoning underlying the enablement rejection is the same as that set forth for the description rejection of OA §7, and our answer is the same.

The specification is believably enabling for the generic claims because

(1) the vertebrate GH family includes members with less than 50% identity to each other (which nonetheless have growth-promoting activity) (see Watahiki (1989) cited at P15, L37);

(2) Applicants have made GH mutants which are only 66% identical yet have GH antagonist activity (compare applicants HGH and BGH mutants and see P14, L19-24); and

(3) the specification teaches the use of alanine-scanning mutagenesis (P17, L7-15); P25, L21-23), homologue-scanning mutagenesis (P16, L34-P17, L7; P25, L17-21), multiple alignment of homologous sequences (P17, L16-22 and 35-37; P18, L3-4; P24, L26-36); general knowledge of which AA exchanges are usually tolerated in protein families (P23, L14-38; P25, L33-P28, L10); combinatorial mutagenesis (P22, L6-P23, L4); other selective mutagenesis (P28, L13-17); knowledge of the 3D structure (P25, L5-16), and other techniques, to inform the decision of which residues to replace, and with what.

3. Definiteness

Finally, OA §10 questions the definiteness of "purified or naturally occurring" (see above), "first vertebrate growth hormone" (as undefined), "differs there from solely in that" (as

contradicting other limitations) "coding sequence encoding" (as redundant) "an amino acid substitution of an amino acid" (as redundant), "at the position corresponding to position 119 of bovine growth hormone" (as the numbering allegedly could change), and "said position" of claim 108 or 107 (not clear which position is intended).

With regard to "first vertebrate growth hormone", note that "first" was our substitute for "reference". The specification plainly contemplates comparing the mutant GH to naturally occurring GHs, the latter hence acting as points of reference.

We do not agree that "differs therefrom solely in that" is contradictory. The recited modifications which follow are those allowed by "solely", not exceptions to it.

With regard to the allegedly redundant language, it was suggested to us by a prior Examiner in a prior case of this family and we suggest that it be retained for the sake of consistency.

In connection with "position 119", we have added a reference to the "glycine". Likewise, we have amended claim 108 to clarify "said position", although we think the meaning was already clear in both cases.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 10, 29, 66, 81, 88, 89, 107-112 have been amended as follows:

10 (twice amended). A [purified or] non-naturally occurring DNA molecule comprising a coding sequence encoding a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first vertebrate growth hormone residue where

(i) a second vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first vertebrate growth hormone's receptor of a single substitution mutant of the first vertebrate growth hormone,

wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first vertebrate growth hormone,

(c) a deletion of a residue which is not part of the alpha helixes of said vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and

(d) a deletion of a residue found in said first vertebrate growth hormone but deleted in a second reference vertebrate growth hormone,

said polypeptide having growth hormone receptor antagonist activity,

with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

29 (thrice amended). A [purified or] non-naturally occurring DNA molecule which comprise a coding sequence which encodes a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence comprising residues corresponding to residues 96-133 of bovine growth hormone which sequence is at least 50% identical to the amino acid sequence of a first vertebrate growth hormone, and wherein the amino acid position corresponding to amino acid Gly 119 of bovine growth hormone is an amino acid other than glycine or alanine, said polypeptide having growth hormone receptor antagonist activity, with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

66 (amended). A [purified or] non-naturally occurring DNA molecule comprising a coding sequence encoding a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first reference vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue where

(i) a second reference vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first reference vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first reference vertebrate growth hormone's receptor of a single substitution mutant of the first reference vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at

least 10% of the binding affinity of the wild-type first reference vertebrate growth hormone,

(c) a deletion of a residue which is not part of the alpha helixes of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and

(d) a deletion of a residue found in said first reference vertebrate growth hormone but deleted in a second reference vertebrate growth hormone,

said polypeptide having growth hormone receptor antagonist activity,

with the proviso that said first and second reference vertebrate growth hormones are both mammalian growth hormones.

81 (amended). A [purified or] non-naturally occurring DNA molecule comprising a coding sequence encoding a growth hormone receptor antagonist which is a mutant polypeptide comprising an amino acid sequence, said polypeptide being a mutant of a vertebrate growth hormone, the amino acid sequence of said mutant of a vertebrate growth hormone comprising a substitution of the glycine of said vertebrate growth hormone corresponding to Gly119 of bovine growth hormone, with an amino acid other than glycine or alanine,

said polypeptide having growth hormone receptor antagonist activity,

with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

88 (amended). A method of reducing growth hormone activity

in a mammalian subject which comprises administering to the subject a DNA molecule according to claim 81 [comprising a coding sequence encoding a mammalian growth hormone receptor antagonist which is a polypeptide], under conditions conducive to the integration of said DNA into the genome of one or more cells of said subject, said subject subsequently expressing a growth hormone activity-antagonizing and pharmaceutically acceptable amount of said polypeptide, said polypeptide having growth hormone antagonist activity in said subject,

[where said polypeptide is a mutant polypeptide comprising an amino acid sequence, said polypeptide being a mutant of a vertebrate growth hormone, the amino acid sequence of said mutant of a vertebrate growth hormone comprising a substitution of the glycine of said vertebrate growth hormone corresponding to Gly119 of bovine growth hormone, with an amino acid other than glycine or alanine,]

said polypeptide having mammalian growth hormone receptor antagonist activity,

whereby the growth hormone activity in said subject is reduced.

89. The method of claim [81] 88 wherein the mammal suffers from an excessive growth rate.

107 (amended). A [purified or] non-naturally occurring DNA molecule comprising a coding sequence encoding a vertebrate growth hormone variant comprising an amino acid substitution of an amino acid, other than glycine or alanine, for the amino acid of said vertebrate growth hormone at the position corresponding to the glycine at position 119 of bovine growth hormone, wherein the growth hormone variant has vertebrate growth hormone inhibitory activity, with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

108 (amended). The DNA molecule of claim 107 where said variant differs from the vertebrate growth hormone solely at said position corresponding to the glycine at position 119 of bovine

growth hormone.

109 (amended). A [purified or] non-naturally occurring DNA molecule comprising a coding sequence encoding a vertebrate growth hormone variant comprising lysine at the position corresponding to the glycine at position 119 of bovine growth hormone, wherein the growth hormone variant has vertebrate growth hormone inhibitory activity.

110 (amended). A [purified or] non-naturally occurring DNA molecule comprising a coding sequence encoding a vertebrate growth hormone variant comprising arginine at the position corresponding to the glycine at position 119 of bovine growth hormone, wherein the growth hormone variant has vertebrate growth hormone inhibitory activity.

111 (amended). A [purified or] non-naturally occurring DNA molecule comprising a coding sequence encoding a vertebrate growth hormone variant comprising proline at the position corresponding to the glycine at position 119 of bovine growth hormone, wherein the growth hormone variant has vertebrate growth hormone inhibitory activity.

112 (amended). A [purified or] non-naturally occurring DNA molecule comprising a coding sequence encoding a vertebrate growth hormone variant comprising tryptophan at the position corresponding to the glycine at position 119 of bovine growth hormone, wherein the growth hormone variant has vertebrate growth hormone inhibitory activity.

Claims 114-117 have been added.

Claims 35, 36 and 62 were cancelled.